

# COMBINATORIAL THERAPIES FOR THE TREATMENT OF NEOPLASIAS USING THE OPIOID GROWTH FACTOR RECEPTOR

## CROSS-REFERENCE TO RELATED APPLICATIONS

**[0001]** This application is a Continuation Application of U.S. Ser. No. 15/159,334, filed May 19, 2016, which is a Continuation Application of U.S. Ser. No. 13/660,129 filed Oct. 25, 2012, now U.S. Pat. No. 9,375,458, issued Jun. 28, 2016, which is a Continuation Application of U.S. Ser. No. 13/020,077 filed Feb. 3, 2011, which is a Continuation Application of U.S. Ser. No. 11/510,682 filed Aug. 25, 2006, now U.S. Pat. No. 8,003,630 issued Aug. 23, 2011, which is a Continuation of International Application No. PCT/US05/05268 filed Feb. 21, 2005 which claims priority to Ser. No. 60/548,021 filed Feb. 26, 2004, herein incorporated by reference in their entirety.

**[0002]** This application is a Continuation Application of U.S. Ser. No. 11/061,932 filed Feb. 21, 2005, which claims priority to Ser. No. 60/548,021 filed Feb. 26, 2004, herein incorporated by reference in their entirety.

## FIELD OF THE INVENTION

**[0003]** The invention relates generally to therapeutic formulations for use in the treatment of neoplasias. More specifically, the invention relates to pharmaceutical formulations comprised of chemotherapeutic agents and biotherapeutic agents for treating neoplasias. Methods for treating neoplasias by administering combinatorial formulations of neoplasia-treating agents, such as chemotherapeutic and/or radiation, along with biotherapeutic agents are also disclosed.

## DESCRIPTION OF RELATED ART

**[0004]** Cancer is the second leading cause of death in the United States, surpassed only by heart disease. According to the American Cancer Society, approximately 556,000 Americans die from cancer each year—an average of more than 1,500 cancer deaths each day (Jemal, A. et al., *CA Cancer J. Clin.*, 55, 10-30, 2005). Of the different cancers not including the skin cancers, lung cancer is the leading cause of cancer death for both men and women; breast cancer is the second leading cause of cancer death in women; prostate cancer is the second leading cause of cancer death in men and colorectal cancer is the third most frequently diagnosed form of cancer.

**[0005]** Pancreatic cancer is the most lethal human cancer with median survival for all stages of pancreatic cancer being less than 3-5 months from diagnosis. (*CA Cancer J. Clin.*, 2004 54:8-20). The five-year survival rate is 3% or less. In spite of treatment efforts of surgery, radiation, and chemotherapy, the survival rate remains unchanged. (*CA Cancer J. Clin.*, 2004) The incidence of pancreatic cancer is only 0.01% in the United States, but it is associated with the deaths of over 30,000 individuals each year, making this the most common in terms of cancer mortality. (Jemal, A. et al., *CA Cancer J. Clin.*, 55, 10-30, 2005). Approximately 85-90% of symptomatic patients have advanced disease as a result of local infiltration or metastases at the time of diagnosis, and the prognosis for these individuals is extremely poor. (*CA Cancer J. Clin.* 2005). Although some advances in treatment have been made that include surgery,

chemotherapy, radiation therapy, immunotherapy, and hormonal therapy, pancreatic cancer remains a profound challenge in terms of prevention, diagnosis, prognosis and therapy.

**[0006]** At the time of diagnosis, up to around to around about 20% of pancreatic tumors can be removed by surgery. (*Lancet* 2004; 363:1049-57). When the tumor is confined to the pancreas but cannot be removed, a combination of radiotherapy and chemotherapy is usually performed. When the tumor has metastasized to other organs, such as the liver, chemotherapy alone is usually used. The standard chemotherapy agent is gemcitabine, but other drugs may be used. Gemcitabine essentially provides only palliative improvement in patients.

**[0007]** Head and neck cancer is the sixth ranking cancer in the world, and the third most common neoplasia in developing nations. In the United States, the incidence of cancer of the aerodigestive tract accounts for approximately 40,000 new cases each year, with over 11,000 fatalities recorded annually (Jemal, A. et al., *CA Cancer J. Clin.*, 55, 10-30, 2005). More than 90% of head and neck cancers are squamous cell carcinomas (SCCHN), with the oral cavity and pharynx being the most common sites for SCCHN, followed by the larynx. Surgery, radiotherapy and chemotherapy, and combinations thereof, are all considered for treatment. Unfortunately, there is over a 50% chance of recurrence of SCCHN within two years, and the five-year survival is approximately 50% for all sites and stages. Moreover, in the last twenty-five years, the five-year survival of patients with SCCHN has not changed appreciably (Jemal, A. et al., *CA Cancer J. Clin.*, 55, 10-30, 2005).

**[0008]** Peptide growth factors and their receptors have been implicated in SCCHN and pancreatic cancer, as well as in a number of other cancers (Sugerman, P. B. et al., *Oral Dis.*, 1, 172-188, 1995). Some of the peptides found to be expressed in pancreatic cancer and SCCHN include epidermal growth factor (EGF), transforming growth factors  $\alpha$  and  $\beta$ , basic fibroblast growth factor (bFGF), insulin-like growth factor (IGF), platelet derived growth factor (PDGF), and keratinocyte growth factor (KGF).

**[0009]** One group of peptides, the endogenous opioids, are believed to be important in the growth of normal, neoplastic, renewing and healing tissues, as well as in prokaryotes and eukaryotes (Zagon, I. S. et al., In: *Cytokines: Stress and Immunity*. Plotnikoff N P et al., (eds). CRC Press, Boca Raton, Fla., pp. 245-260, 1999). Met-enkephalin, an endogenous opioid peptide, is directly involved in growth processes, and serves as a negative regulator in a wide variety of cells and tissues (Zagon, I. S. et al., In: *Receptors in the Developing Nervous System*. Vol. 1. Zagon, I. S. and McLaughlin, P. J. (eds). Chapman and Hall, London, pp. 39-62, 1993). In view of its function (growth) and distribution (neural and non-neural), the peptide has been termed opioid growth factor (OGF).

**[0010]** Cancer chemotherapeutic agents are used for their lethal action to cancer cells. Unfortunately, few such drugs differentiate between a cancer cell and other proliferating cells. Chemotherapy generally requires use of several agents concurrently or in planned sequence. Combining more than one agent in a chemotherapeutic treatment protocol allows for: (1) the largest possible dose of drugs; (2) drugs that work by different mechanisms; (3) drugs having different toxicities; and (4) the reduced development of resistance.